98-390318/34 B03 FABR 97.01.15

FABRE MEDICAMENT SA PIERRE *FR 2758328-A1

97.01.15 97FR-000337 *(98.07.17)* C07D 401/12, A61K 31/445, 31/495, C07D 295/18 (C07D 211:34, 295:18, 401/12) (C07D 207:09, 401/12, 295:18) (C07D 211:34, 401/12, 211:64)

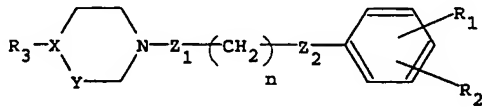
New aryl-substituted cyclic amine compounds - used as selective 5-HT-1D and 5-HT-1B receptor antagonists or partial agonists, e.g. for treating depression, anxiety or cancer

C98-118102

Addnl. Data: LAMOTHE M, HALAZY S

B(7-D5, 7-D11, 14-H1, 14-J1) .4

Aryl-substituted piperazine, homopiperazine, piperidine or tetrahydropyridine derivatives of formula (I) and their hydrates, solvates and bio-precursors, including geometric and optical isomers and their mixtures (especially racemates), are new.



(I)

R_1 = 1-(R_4)-piperidin-4-yl, 1-(R_4)-pyrrolidin-2-ylmethyl, -Q-$(CH_2)_m$-NR_4R_5, -C≡C-CH_2-NR_4R_5 or -CH=CH-CH_2-NR_4R_5;
R_4, R_5 = H or 1-6C alkyl;
Q = O, NH or CH_2;
m = 2-4;
R_2 = H, Cl, OH, OMe or Me;
R_1 is in the ortho- or meta-position of the phenyl ring with respect to Z_2 and R_2 is in any other position of the ring;
X-Y = N-CH_2, N-CH_2CH_2, CR_6-CH_2 or C≡CH;
Z_1 = CH_2 or CO;
Z_2 = O or NH;
n = 0-6,
provided that n is other than 0 if Z_1 = CH_2;
R_3 = Ar or Ar-alkyl (e.g. benzyl, phenyl or phenylpropyl), or
R_3 can also = OR'_3, SR'_3, NHR'_3, COR'_3 or $CH(OH)R'_3$ if X-Y = CR_6-CH_2; or
R_3 can also = COR'_3 or $CH(OH)R'_3$ if X-Y = C≡CH;
Ar = phenyl, naphthyl, pyridyl or tetrahydronaphthyl (all optionally

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substituted by one or more of 1-5C alkyl, halo, OH, OR_7, SR_7, CF_3, CH_2CF_3, NO_2, CN, COR_7, $COOR_7$, NHR_7, $NHCOR_7$, $NHCOOR_7$, $NHSO_2R_7$ and SO_2R_7);
R_7 = H or 1-5C alkyl;
R'_3 = Ar or Ar-alkyl;
R_6 = H, Cl, F, Br, OH, CN, NO_2, R'_6, OR'_6, NHR'_6, COR'_6, $CH(OH)R'_6$, $COOR'_6$, $NHCOR'_6$, $NHCOOR'_6$, $NHSO_2R'_6$ or OCONHR'$_6$;
R'_6 = 1-5C alkyl, Ar' or Ar'-alkyl;
Ar' = phenyl, naphthyl or pyridyl (all optionally substituted by one or more of 1-5C alkyl, halo, OH, OR_8, SR_8, CF_3, CH_2CF_3, NO_2, CN, COR_8, $COOR_8$, NHR_8, $NHCOR_8$, $NHCOOR_8$, $NHSO_2R_8$ and SO_2R_8);
R_8 = 1-5C alkyl;
provided that if R_3 = OR'_3, SR'_3 or NHR'_3, then R_6 = carbon-containing substituent other than CN.

MORE SPECIFICALLY

X-Y = N-CH_2 or CH-CH_2;
R_3 = phenyl, naphthyl, phenethyl or phenylpropyl (all optionally substituted by one or more of Me, OMe, F, Cl, CF_3 or CN);
R_2 = H, OMe or OH.

USE

(I) are 5HT-1D and 5HT-1B receptor antagonists or partial agonists, and are useful for treating or preventing disorders associated with serotonin, e.g. CNS and cell proliferation disorders or pain.

They are especially used for treating or preventing depression, compulsive-obsessive disorders, anxiety, panic attacks, schizophrenia, aggression, bulimia, alcoholism, pain, neuro-degenerative diseases (e.g. Parkinson's and Alzheimer's disease) or cancer (all claimed). Other disorders which may be treated include headache of various origins, migraine, movement disorders, agoraphobia, memory disorders, dementia, amnesia, appetite disorders, sexual dysfunction, endocrine disorders (e.g. hyperprolactinaemia), vasospasm, hypertension and gastrointestinal disorders involving motility and secretion.

Daily dose for adults is 0.001-1 (preferably 0.005-0.25) g, preferably orally. Claimed pharmaceutical compositions containing (I) optionally also contain a further antidepressant active agent, especially milnacipran and/or a 5HT-1A antagonist.

ADVANTAGE

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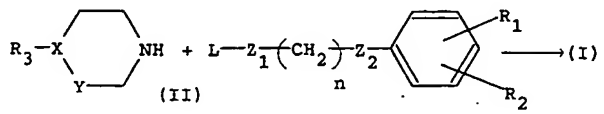
(I) are potent and selective antagonists and partial agonists of human 5HT-1D and 5HT-1B receptors, having especially high selectivity for such receptors relative to 5HT-1A, 5HT-1C, 5HT-2, α_1, α_2 and D_2 receptors.

PREPARATION

The following processes are claimed.

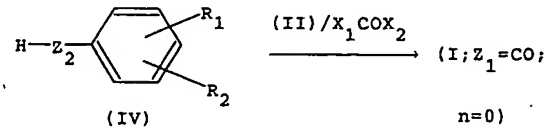
(a)



(II)

L = leaving group (such as Br, Cl, I, mesylate, triflate or tosylate) if Z_1 = CH_2; or OH, Cl or residue of an activated COOH group if Z_1 = CO.

(b)



(IV)

X_1, X_2 = leaving groups such as Cl or $OCCl_3$.

EXAMPLE

A solution of 1.33 g 3-(N-tert, butoxycarbonyl-N-(2-dimethylaminoethyl)-amino)-4-methoxy-3-aniline and 600 µl NEt_3 in 10 ml CH_2Cl_2 was treated under N_2 at 0°C with a solution of 420 mg triphosgene in 10 ml CH_2Cl_2, stirred at room temperature for 30 minutes, treated with a solution of 1.23 g 4-(2,3-dimethylphenyl)-piperazine and 600 µl NEt_3 in 10 ml CH_2Cl_2 and stirred for 12 hours at room temperature. Work-up and chromatographic purification gave 1.21 g (53%) of (4-(2,3-dimethyl-phenyl)-piperazin-1-yl)-N-(3-(N-

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tert. butoxycarbonyl-N-(2-dimethylaminoethyl)-amino)-4-methoxy-phenyl)-amide.

A solution of 1.2g of the product in 65 ml CH_2Cl_2 was treated under N_2 with 44 ml CF_3COOH, stirred for 24 hours at room temperature and evaporated. Work-up and chromatographic purification gave 870 mg (89%) of (4-(2,3-dimethyl-phenyl)-piperazin-1-yl)-N-(3-(2-dimethylaminoethylamino)-4-methoxy-phenyl)-amide, which was converted into the fumarate by reaction with fumaric acid in methanol.

BIOLOGICAL DATA

(I) had IC_{50} values 10-1,000 nM for inhibition of the sumatriptan-stimulated incorporation of labelled thymidine into C_6 type glial cells transfected with the 5HT-1D and 5HT-1B receptor genes. No specific values for individual compounds are given. (AB)
(45pp2400DwgNo.0/0)

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